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# Opposite outcomes of coinfection at individual and population scales

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Coinfecting parasites and pathogens remain a leading challenge for global public health due to their consequences for individual-level infection risk and disease progression. However, a clear understanding of the population-level consequences of coinfection is lacking. Here, we constructed a model that includes three individual-level effects of coinfection: mortality, fecundity, and transmission. We used the model to investigate how these individual-level consequences of coinfection scale up to produce population-level infection patterns. To parameterize this model, we conducted a 4-y cohort study in African buffalo to estimate the individual-level effects of coinfection with two bacterial pathogens, bovine tuberculosis (bTB) and brucellosis, across a range of demographic and environmental contexts. At the individual level, our empirical results identified bTB as a risk factor for acquiring brucellosis, but we found no association between brucellosis and the risk of acquiring bTB. Both infections were associated with reductions in survival and neither infection was associated with reductions in fecundity. The model reproduced coinfection patterns in the data and predicted opposite impacts of coinfection at individual and population scales: Whereas bTB facilitated brucellosis infection at the individual level, our model predicted the presence of brucellosis to have a strong negative impact on bTB at the population level. In modeled populations where brucellosis was present, the endemic prevalence and basic reproduction number ( $R_0$ ) of bTB were lower than in populations without brucellosis. Therefore, these results provide a data-driven example of competition between coinfecting pathogens that occurs when one pathogen facilitates secondary infections at the individual level.

African buffalo | brucellosis | tuberculosis | coinfection | competition

Over one-sixth of the global human population is estimated to be affected by coinfection [concurrent infection by multiple pathogens (1)]. Their ubiquity includes over 270 pathogen taxa and many important chronic infections, such as hepatitis-C, HIV, TB, and schistosomiasis (1–3). Mounting evidence suggests that coinfecting pathogens can interact within the host to influence the individual-level clinical outcomes of infection (4, 5). These interactions may also influence the spread of infections at the population level (6, 7). Understanding the effects of coinfection at both levels may, therefore, be fundamental to the success of integrated treatment and control programs that target multiple infections (8, 9).

One challenge to predicting the epidemiological consequences of coinfection is that the mechanisms of parasite interaction—and their resulting changes to susceptibility or disease progression—occur within the host, while patterns relevant for disease control occur within a population (10). Bridging these individual and population scales requires synthesizing multiple, individual-level processes across natural demographic and environmental variation. For example, in an ecosystem with more than one pathogen, infection with one pathogen may be one of

the best predictors of individual-level risk for infection with a second pathogen (11, 12), resulting in increased or decreased transmission. Coinfecting pathogens may also moderate the individual-level survival and fecundity costs of infection (4, 13). However, the population-level consequences of coinfection are influenced by the net effects of these potentially nonlinear individual-level processes (14, 15).

At the population level, theoretical studies have highlighted the range of dynamics generated by coinfecting pathogens (6, 16, 17). Even for unrelated pathogens, coinfection can dramatically modify infection dynamics through ecological mechanisms such as convalescence and disease-induced mortality (15, 18–21). This theoretical work builds on a detailed database of childhood infections, thereby providing a data-driven understanding of coinfection dynamics for acute, immunizing infections. In contrast, data and theory on the effects of coinfection with long-lasting infections are limited (but see ref. 22). Chronic coinfections are of particular interest in this context because they are responsible for the majority of coinfections (1) and have the potential to dramatically alter infection patterns (14). Their protracted presence in the host brings increased complexity to pathogen interactions, challenging model development and

## Significance

Infection with multiple parasite species is common and the majority of coinfections involve at least one long-lasting infection. Our data-driven model of chronic coinfection dynamics shows that accurate prediction at the population level requires quantifying both the individual-level transmission and mortality consequences of coinfection. The infections characterized in this study compete at the population level. When one pathogen facilitates both the transmission and progression of the second pathogen, the prevalence of the first pathogen is reduced. This mechanism of competition is unique compared with previously described mechanisms and occurs without cross-immunity, resource competition within the host, or convalescence. We recommend assessing the generality of this mechanism, which could have important consequences for other chronic, immunosuppressive pathogens such as HIV or TB.

Author contributions: E.E.G., R.S.E., J.M., V.O.E., and A.E.J. designed research; E.E.G., R.S.E., and J.M. performed research; E.E.G., R.S.E., J.M., B.R.B., V.O.E., and A.E.J. analyzed data; E.E.G., R.S.E., J.M., B.R.B., J.M.S., R.S.S., V.O.E., and A.E.J. wrote the paper; and E.E.G., B.R.B., J.M.S., R.S.S., V.O.E., and A.E.J. collected the data.

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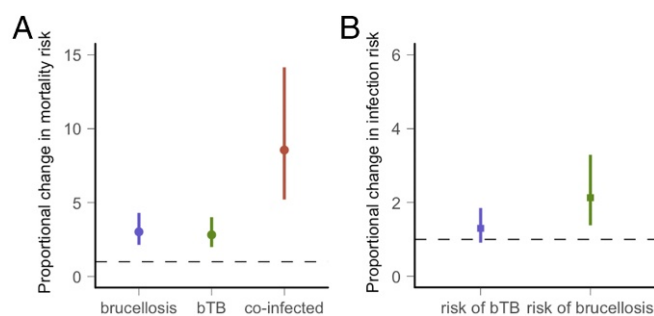
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The consequences of coinfection on infection risk were asymmetric, with bTB facilitating brucellosis infection but not vice versa (Fig. 2B and [SI Appendix, section 1, Table S2](#)). Approximate brucellosis incidence rates were 0.05 (18 infections/340 animal years) in uninfected buffalo compared with 0.08 (8 infections/104 animal years) in buffalo with bTB ([SI Appendix, section 1, Fig. S2](#)). Approximate bTB incidence rates were 0.08 (27 infection/340 animal years) in uninfected buffalo and 0.07 (9 infections/138 animal years) in buffalo with brucellosis. After accounting for demographic covariates in a Cox proportional hazards regression model, brucellosis infection risk





**Fig. 2.** Parameter estimation based on Cox proportional hazards analyses of the cohort study. (A) The predicted median and SE for the proportional change in mortality when buffalo are infected with brucellosis or bTB or coinfectd relative to uninfected buffalo. (B) The predicted estimates for the proportional change in infection risk when buffalo are infected with another pathogen relative to the risk in uninfected buffalo. The dashed line indicates no change in risk.

was 2.09 (95% CI 0.89–4.91) times higher in buffalo with bTB compared with susceptible buffalo. bTB infection risk was similar in uninfected buffalo and buffalo with brucellosis. The association between prior infection with bTB and brucellosis infection risk varied by capture site, with the association between bTB and brucellosis infection risk ranging from no change at one site to a 4.32 (95% CI 1.51–12.37)-fold higher risk at the other site (interaction term for bTB  $\times$  site:  $P$  value = 0.045 and [SI Appendix, section 1, Table S2](#)). The regression model also identified an association between brucellosis infection risk and buffalo age. Early reproductive-aged buffalo had an increased infection risk.

### Population-Level Consequences of Coinfection: Basic Reproduction

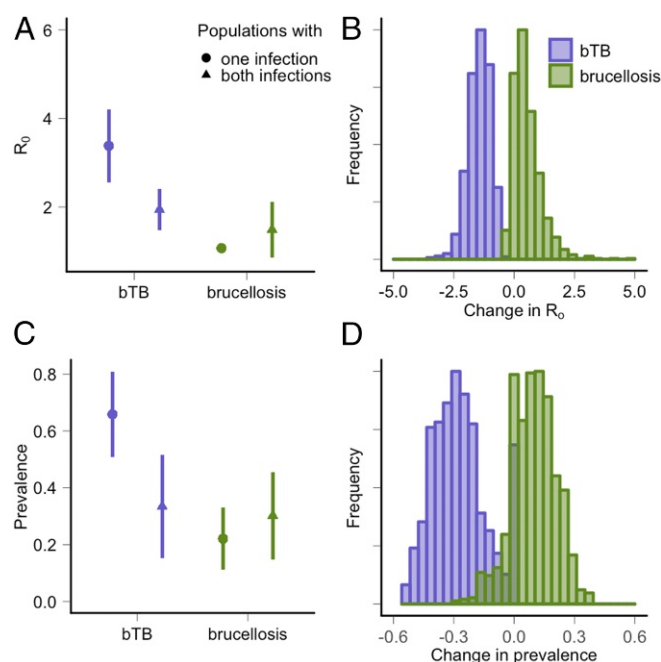
**Number and Prevalence.** We built a disease dynamic model to translate the individual-level effects quantified above into predicted population-level effects of coinfection (Fig. 1 and [SI Appendix, section 2](#)). Our disease model parameterization, therefore, represents increased risk of acquiring brucellosis in early reproductive-aged buffalo and the average effect of bTB on brucellosis infection risk across sites. For example, to represent increased brucellosis infection risk in buffalo with bTB, we specify a higher transmission rate for buffalo with bTB compared with the transmission rate for uninfected buffalo. [SI Appendix, section 2, Tables S3 and S4](#) provides additional detail on model parameterization and defines how the consequences of coinfection quantified in our data analyses were translated into model parameters.

We estimated parameter values for the transmission rate of bTB and brucellosis by minimizing the sum of squared errors between the overall bTB and brucellosis infection prevalence in our data and in an age-matched sample from the model after it had reached equilibrium (*SI Appendix, section 2, Fig. S4*). bTB prevalence in the data was 27% and brucellosis prevalence was 34%. The resulting transmission rate parameters (brucellosis transmission rate in uninfected buffalo, 0.576; brucellosis transmission rate in buffalo with bTB, 1.20; bTB transmission rate in uninfected buffalo and in buffalo with brucellosis, 0.0013; *SI Appendix, section 2, Table S4*) accurately predict the positive association between bTB and brucellosis observed in the data (Fig. 1, *Right, Inset bar plot*) and allow us to predict the prevalence and basic reproduction number in modeled populations with and without coinfection. The basic reproduction number,  $R_0^i$  ( $i = T, B$  for infection with bTB or brucellosis) is defined as the average number of secondary cases generated by a single infection in a susceptible population.

In modeled populations, the presence of brucellosis infection results in large reductions in  $R_0^T$ , with a predicted  $R_0^T = 3.4$

in populations where brucellosis is absent and  $R_0^T = 1.5$  in populations where brucellosis is present. The predicted bTB prevalence is also lower in populations where both pathogens occur, with a bTB prevalence of 65.8% in populations where brucellosis is absent compared with 27.9% when both pathogens co-occur. Conversely, the presence or absence of bTB has only minor effects on the  $R_0^B$  and brucellosis prevalence. To represent uncertainty in the individual-level consequences of coinfection, we used Monte Carlo sampling of the parameters quantified in our statistical analyses (Fig. 2 and *SI Appendix, section 2, Table S5*). Fig. 3 displays the effect of coinfection when uncertainty in input parameters is considered. In this range of parameter values (parameter space), 96% of model trajectories predict a lower bTB prevalence in populations with brucellosis than in populations without brucellosis. In the remaining 4%, brucellosis did not persist in populations with or without coinfection due to high mortality rates and low facilitation rates (*SI Appendix, section 2, Fig. S5*).

To generalize these results, we compared infection prevalence in modeled populations with and without coinfection over a range of parameter values. We manipulated the infection



**Fig. 3.** Model predictions of the reciprocal consequences of coinfection in populations where one or both pathogens occur. Purple represents the model predictions of (A and B)  $R_0$  and (C and D) prevalence for bTB; green represents predictions of  $R_0$  and prevalence for brucellosis. For example, the purple circles and lines represent the median and SE prediction for bTB in populations where only bTB occurs. The purple triangles represent the prediction for bTB in populations where both pathogens are present. We used Monte Carlo sampling to quantify the uncertainty in model outcomes due to uncertainty in the parameters describing the individual-level consequences of coinfection (Fig. 2 and *SI Appendix, section 2*). (A) The estimated  $R_0$  for bTB was lower in populations where brucellosis co-occurs while the estimated  $R_0$  for brucellosis was similar in populations with and without bTB. (B) Histograms showing the difference in  $R_0$  in populations where one or both pathogens are present. For each parameter set, change is calculated as the predicted value of bTB prevalence (purple) or brucellosis prevalence (green) in populations with coinfection subtracted by the predicted value in populations with a single pathogen. (C) The estimated prevalence of bTB was lower in populations where brucellosis co-occurs, while the estimated prevalence of brucellosis was similar in populations with and without bTB. (D) Histograms showing the difference in prevalence in populations where one or both pathogens are present.



risk (e.g., transmission rate) and mortality consequences of coinfection to explore other environmental contexts where the individual-level effects of coinfection may be reduced or exacerbated (Fig. 4). For two pathogens, A and B, the results suggest that pathogen A will have a negative effect on the prevalence of pathogen B if coinfecting individuals have elevated mortality and infection with pathogen A results in reduced or similar susceptibility to pathogen B. In contrast, pathogen A is predicted to have a positive effect on the prevalence of pathogen B if infection results in an increased transmission rate for pathogen B and minimal changes in mortality with coinfection. When coinfection is associated with changes in both the transmission and mortality rates, the population-level consequences of coinfection depend on the type of pathogen considered. Specifically, bTB prevalence is lower in modeled populations with brucellosis for most parameter values while the effect of bTB on brucellosis is more variable.

At the parameter values quantified in our empirical dataset, these results illustrate that the lower bTB prevalence in populations where brucellosis co-occurs is driven by two mechanisms: (i) bTB is associated with increases in the transmission rate of brucellosis but not vice versa and (ii) coinfection is associated with increased mortality. As a result, at the individual level, buffalo infected with bTB are more likely to become infected with brucellosis and die than their uninfected counterparts. The resulting reductions in infection duration mean that the presence of brucellosis is predicted to reduce bTB prevalence at the population level. These results are robust to several important changes in the model structure, including alternative forms of density dependence, a range of values for the model parameters (*SI Appendix, section 2, Figs. S6–S8*), and density- vs. frequency-dependent transmission terms. Model dynamics in all formulations are qualitatively similar, although there is some variation in overall magnitude of change with coinfection.

## Discussion

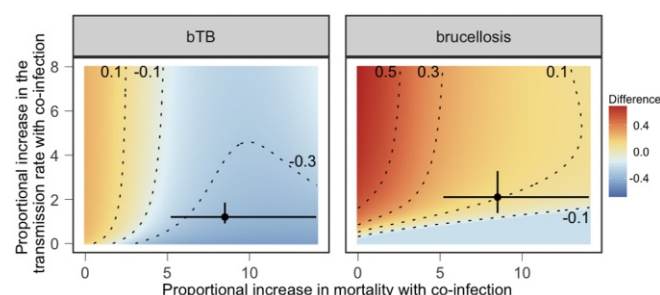
Our study provides a mechanistic understanding of how chronic coinfections mediate each other's dynamics. Model dynamics show that a pathogen can increase or decrease the prevalence of a second pathogen, depending on the net effect of infection on the transmission rate and infection duration of

the second pathogen, the latter via mortality. When infection with one pathogen modifies only the transmission or only the mortality rate of the second pathogen, the prevalence of the second pathogen predictively increases or decreases (Fig. 4 and *SI Appendix, section 2, Figs. S7 and S8*). Previous work has quantified the disease-dynamic consequences of changes in transmission through a range of mechanisms: cross-immunity, antibody-mediated enhancement, immunosuppression, and convalescence (16, 20, 28, 29). Here, we show that transmission and mortality should be considered concurrently, following theoretical predictions (14, 22, 30). When pathogens modify both processes, nonlinear responses mediated through the coinfecting pathogen can have a large impact on population-level disease dynamics.

By exploring the coinfection dynamics of bTB and brucellosis, we also provide a data-driven example of competition between pathogens in a natural population. Here, the mechanism driving competition is different from previously described examples that focus on cross-immunity (29), resource competition within the host (31, 32), or ecological competition by convalescence (20, 21). The mechanism of parasite interaction in these examples occurs when one infection reduces the transmission of the second pathogen. By contrast, in our study system, we did not see a reduced transmission rate for bTB or brucellosis during coinfection. Individuals infected with bTB were associated with a higher rate of acquiring brucellosis in at least one of our sites but appeared to have no effect in the other site. Brucellosis appeared to have no effect on the transmission of bTB (Fig. 2). Because coinfection was associated with elevated mortality, coinfecting individuals were also removed from the population at a faster rate. Competition, therefore, occurs at the population level: bTB is predicted to have a lower prevalence and lower  $R_0^T$  in populations where brucellosis occurs compared with populations without brucellosis.

The model structure in this study is informed by our empirical data. As a result, it incorporates realistic age-specific transmission and mortality rates as well as data-driven estimates of the consequences of coinfection. However, additional detail could be added to our model. Specifically, we do not know the consequences of either infection on the other's infection duration or infectiousness, two processes likely to influence persistent infections (18, 22). We also do not consider genetic variation within our buffalo population that may mediate susceptibility to either pathogen. However, our model's ability to accurately represent coinfection patterns with the mechanisms characterized suggests that we have captured the most important processes. Furthermore, our empirical results account for natural variation in demographic and environmental conditions. Thus, our results highlight the importance of coinfection in generating population-level association patterns relative to environmental or genetic drivers of infection.

Given the ubiquity and documented individual-level impacts of chronic coinfections on the host, these results highlight two core challenges in the design and application of integrated control strategies. First, it remains unclear how commonly competition between coinfecting pathogens is occurring. Understanding which pathogens may be competing in coinfecting host populations is crucial to estimating the costs and benefits of disease control interventions. For example, in the presence of pathogen competition, removing one pathogen may unintentionally lead to a resurgence of or increases in prevalence of a competing pathogen. Our results suggest that competition at the population level can occur between unrelated pathogens and in the absence of competition for shared resources within the host. Competition appears to be strongest when pathogens have asymmetric effects on transmission. Similar asymmetries in transmission occur in HIV–malaria (6) and HIV–HCV coinfections (33), suggesting a role for this mechanism in other systems.



**Fig. 4.** The difference between predicted (Left) bTB or (Right) brucellosis prevalence values in populations where one or both pathogens are present. The axes represent a range of transmission rate and mortality consequences of coinfection. Proportional increases in mortality represent the mortality rate in coinfecting individuals divided by the rate in susceptible individuals. Proportional increases in the transmission rate represent the transmission rate of the focal pathogen in individuals infected with the second pathogen divided by the transmission rate of the focal pathogen for susceptible individuals. Red indicates that the prevalence of the focal pathogen is higher in populations where the second pathogen is present; blue indicates that the prevalence of the focal pathogen is lower in populations where the second pathogen is present; yellow indicates no change. Contour lines indicate changes in prevalence by 20%. Circles and error bars indicate median and SE parameter values estimated in the data.

Second, knowledge on which chronic pathogens are most likely to be influenced by a second infection remains largely theoretical [excluding notable progress with HIV coinfections (6, 22)]. In this study, the immunosuppressive pathogen, bTB (4, 34), was strongly influenced by coinfection at the population level, and our analyses show that bTB prevalence should typically decline in the presence of another chronic pathogen, provided that coinfecting hosts suffer greater mortality. This raises the question of whether there are traits of chronic pathogens (e.g., immunosuppressive effects) that make them more likely to be influenced by the presence of other infections. Studies addressing these questions are urgently needed to target both research and treatment on the pathogens most likely to be influenced by coinfection.

## Materials and Methods

**Model Development.** We developed an age-structured, continuous-time disease-dynamic model to explore the consequences of coinfection on bTB and brucellosis infection (Fig. 1). Animals were classified in six groups: susceptible to both infections (S), infected with bTB only ( $I_T$ ), infected with brucellosis only ( $I_B$ ), coinfecting with both pathogens ( $I_C$ ), persistently infected with brucellosis but no longer infectious ( $R_B$ ), or persistently infected with brucellosis but no longer infectious and coinfecting with bTB ( $R_C$ ). We modeled bTB as a lifelong infection with density-dependent transmission (35). Both singly infected ( $I_T$ ) and coinfecting ( $I_C$ ,  $R_C$ ) buffalo contribute to bTB transmission. Transmission of brucellosis was assumed to be frequency dependent following modeling work in American bison supporting this assumption (36, 37). Across host species, transmission occurs through ingestion of the bacteria shed in association with aborted fetuses, reproductive tissues, or discharges during birthing [cattle (38), elk (39), and bison (40)]. Singly infected ( $I_B$ ) and coinfecting ( $I_C$ ) buffalo contribute to brucellosis transmission. Persistently infected buffalo ( $R_B$ ,  $R_C$ ) do not contribute to brucellosis transmission, but they do test positive for brucellosis infection. We did not consider vertical transmission because serological evidence suggests that it is rare in African buffalo (41) and experimental evidence for vertical transmission varies by host species [e.g., elk (39)]. Buffalo populations experience density-dependent recruitment, which we modeled with a generalized Beverton–Holt equation (42). This two-parameter representation of density dependence gives a stable age structure and relatively constant population size (ref. 43 and *SI Appendix*, section 2, Fig. S3). A full description of the model is provided in *SI Appendix*, section 2.

The individual-level consequences of coinfection can be summarized by four individual-level processes: (i) the effects of prior infection with brucellosis on the rate individuals acquire bTB infection, (ii) the effects of prior infection with bTB on the rate individuals acquire brucellosis infection, (iii) the effects of coinfection on the per capita mortality rate, and (iv) the effects of coinfection on the per capita birth rate. To investigate the consequences of these four individual-level processes on disease dynamics, we quantified the median values of these rates in susceptible, singly infected, and coinfecting buffalo. Transmission rates, mortality rates, and the proportional reductions in fecundity with infection are allowed to be age dependent, but recovery and recrudescence are assumed to be independent of age.

**Individual-Level Data and Parameter Estimation.** We conducted a longitudinal study of 151 female buffalo to estimate the consequences of bTB and brucellosis infection. Buffalo were captured at two locations in the south-eastern section of Kruger National Park, radio collared for reidentification,

and recaptured biannually at ~6-mo intervals until June–October 2012. During each capture, we recorded brucellosis infection status, bTB infection status, age, and the animals' reproductive status. Brucellosis testing was conducted with an ELISA antibody test and bTB testing was conducted with a gamma-IFN assay (44, 45). Detailed methodological descriptions of our capture and disease testing protocols are provided in *SI Appendix*, section 3. Animal protocols for this study were approved by the University of Georgia (UGA) and Oregon State University (OSU) Institutional Animal Care and Use Committees (UGA AUP A2010 10-190-Y3-A5 and OSU AUP 3822 and 4325).

We assessed the effects of coinfection on median mortality rates and the median rate at which animals acquired infection by analyzing our longitudinal time-to-event data using semiparametric Cox models where an individual's covariates representing infection change over time. Specifically, we fitted three regression models to predict three events: the time to mortality in uninfected, bTB+, brucellosis+, and coinfecting individuals; the time to infection with brucellosis in buffalo with and without bTB; and the time to infection with bTB in buffalo with and without brucellosis. In all analyses, we included age and initial capture site as time-independent, categorical variables and infection status as a time-dependent explanatory variable. We also evaluated whether the association between brucellosis and bTB varied by age or site by including interactions terms between bTB and each environmental variable.

**Model Evaluation and Inference.** Parameter values for the transmission rate of bTB and brucellosis were estimated by fitting the model to the overall prevalence estimate for bTB and brucellosis in the study population. Our data do not represent a random sample because buffalo aged over the course of the study, with a median age of 3.4 y in buffalo initially captured in June–October 2008. We therefore calculated the overall prevalence for each pathogen after randomly sampling one time point for each buffalo. We estimated the overall prevalence in the study population as the median prevalence in 1,000 replicate samples. We use the prevalence calculated for all buffalo in this study regardless of their initial capture location because prevalence was similar at both locations, herds move and mix within and between sites, and site-specific parameters did not change the qualitative conclusion of this work (*SI Appendix*, section 2, Fig. S9). Model estimates of prevalence were calculated numerically using the deSolve package (46). We calculated prevalence in the model after it had reached equilibrium by representing bTB prevalence as  $\pi_T = (I_T + I_C + R_C) / (S + I_T + I_C + R_C + I_B + R_B)$  and brucellosis prevalence as  $\pi_B = (I_B + R_B + I_C + R_C) / (S + I_T + I_C + R_C + I_B + R_B)$ . The transmission rates of both pathogens were estimated by numerically minimizing the sum of squared differences between the prevalence estimates for bTB and brucellosis in the data and in age-matched estimates of prevalence from the model. We used the Nelder–Mead algorithm implemented with the optim function in R to minimize this function. We evaluated our model by comparing its ability to recreate coinfection patterns in the data, as only the overall prevalence of both pathogens was used for fitting (Fig. 1). We calculated  $R_0$  numerically using the next-generation method (47).

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